Supramolecular Layers and Versatile Packing Modes: the Solid State Behavior of \textit{ortho}, \textit{ortho}-linked Bisphenols

André U. Augustin,\textsuperscript{a,\dagger} Felix Katzsch,\textsuperscript{a} Stephen H. Prior,\textsuperscript{b}

Tobias Gruber\textsuperscript{*}, \textsuperscript{a, c}

\textsuperscript{a} Institute of Organic Chemistry, TU Bergakademie Freiberg, Leipziger Straße 29, 09599 Freiberg/Sachsen, Germany

\textsuperscript{b} School of Chemistry, University of Lincoln, Joseph Banks Laboratories, Green Lane, Lincoln LN6 7DL, United Kingdom.

\textsuperscript{c} School of Pharmacy, University of Lincoln, Joseph Banks Laboratories, Green Lane, Lincoln LN6 7DL, United Kingdom. E-mail: tgruber@lincoln.ac.uk; Tel: +44 152 283 7396

\dagger Current address: Institute of Organic Chemistry, TU Braunschweig, Hagenring 30, 38106 Braunschweig, Germany.
Graphical abstract:

Abstract

A series of ortho-ortho-linked bisphenols featuring electron-withdrawing groups (EWGs) attached to the phenolic rings is reported. Their respective molecular structures and packing behaviors have been studied by X-ray diffraction, comparatively discussed and put into relation with the unsubstituted mother compound. Except for the mother compound, the molecular structures of all bisphenols studied here exhibit distorted aromatic moieties. Hence, the substituents studied here prevent proximal positioning of phenolic units and the formation of strong O–H···O hydrogen bonds. In the packing of the underivatized bisphenol we found a strand-like molecular arrangement featuring strong O–H···O hydrogen bonds and extensive edge-to-face contacts (C–H···π) between the bisphenol molecules. The introduction of EWGs to the aromatic moieties changes these intermolecular interactions into face-to-face contacts resulting either in bisphenol stacks or handshake-like motifs between two bisphenol molecules. In both cases, the C–H···π interactions are more or less replaced by C–H···O contacts as the prevalent non-covalent interaction. In the packing of two nitro bisphenols in their DMSO inclusion compounds an exciting layered arrangement is observed, which also matches with the pronounced foliated habitus of their crystals. Additionally, proton NMR was used to establish the binding coefficients between the respective bisphenols and DMSO in solution.

Highlights

*Ortho-ortho*-linked bisphenols featuring electron-withdrawing groups are reported.

The substituted bisphenols studied here exhibit distorted aromatic moieties.

Electron-withdrawing groups at the aromatic moieties favor face-to-face contacts.

Two of the bisphenols develop molecular layers matching with the crystal habitus.

Keywords:

Bisphenol, Single crystal X-ray structure, Layered material, DMSO inclusion, C–H···π interaction
**Introduction**

For decades, bisphenols, *i.e.* condensation products of phenols and aldehydes or ketones, have been well-known educts for the production of a wide range of polymers. They are of special interest for the preparation of epoxy resins and polycarbonates important in the manufacture of everyday products such as electronic devices, water pipes, bottles, coatings, and many others. Some of these bisphenol polymers are believed to disintegrate into respective monomers, which potentially have an impact on human health. Of special concern in this respect is their estrogenic activity, which is very much related to the nature of the bridging group as well as linkage and substitution pattern of the aromatic units. The bioavailability, thus the ecological effectiveness, of bisphenols is thereby directly connected to their molecular conformations. Bisphenol A and bisphenol F are well-researched members of the bisphenol family, exhibiting a *para-para*-substitution pattern of the phenolic units. Related bisphenols featuring an *ortho-ortho*-linkage are also studied due to their biological activity, although reports on the respective solid state behavior are rare.

In this paper, we report on bisphenols with electron-withdrawing groups (EWGs) attached to the phenolic rings and how these modify the respective molecular structure and intermolecular interactions. A special emphasis lies therefore on the conformational parameters of the molecules and the packing motifs. Each of the title compounds features an *ortho-ortho*-substitution at the phenol units with –NO$_2$ and –COOMe moieties being attached in *para*-position (1-7). Some representatives have already been applied in the synthesis of calixarenes and related compounds or proved as useful building blocks for more elaborate structures, in biology as well as in medicine.

**Results and discussion**

**Synthesis**

Bisphenol 1 has been synthesized from 4-nitrophenol and formaldehyde in 86 % yield following literature procedures. Subsequent treatment with boric acid, potassium bromide and hydrogen peroxide similar to Chaudhuri *et al.* delivered 2 (92 % yield), etherification of 2 with methyl iodide and potassium carbonate in acetone yielded 96 % of 3. Bisphenols 4 and 5 have been prepared according to the literature in 70 % and 95 % yield, respectively. Bisaldehyde 7 has been synthesized from methyl 4-hydroxybenzoate, which was dimerized with formaldehyde under acidic conditions in the first step to give 6 (87 % yield), which was then formylated following a modified Duff procedure (88 % yield) (Scheme 1). The inclusion compounds of 1 and 2 with dimethylsulfoxide (DMSO) (1a and 2a, resp.) have been obtained by slow evaporation of the respective solutions in DMSO.
Worth noting is the high chemical stability of the acetal groups in 4 when heated with different mineral acids. In opposition to the literature describing the hydrolysis of the acetylated monomer (9) (Scheme 2), the respective hydrolysis product of 4 featuring four free hydroxyl groups could not be obtained. Moreover, neither ring opening chlorination nor the related bromination have been successful. The applied conditions are summarized in Table S1 (ESI).

Scheme 2 Reference compounds 8-11 including a general numbering scheme for the here presented bisphenols.
**Table 2**  Crystal data and selected details of the data collection and refinement calculations of compounds 1a, 2a and 4-8

<table>
<thead>
<tr>
<th>Compound</th>
<th>1a</th>
<th>2a</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
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<tbody>
<tr>
<td>empirical formula</td>
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<td>C₆H₁₂Br₂N₂O₆ · 2 C₃H₇OS</td>
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<td>C₇H₁₁N₆O₈</td>
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<td>formula weight</td>
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<td>monoclinic</td>
<td>triclinic</td>
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<td>P-1</td>
<td>P2₁/n</td>
<td>P-1</td>
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<td>P2₁/c</td>
<td>P2₁/c</td>
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<tr>
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<td>10.1667(2)</td>
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<td>2</td>
<td>4</td>
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<td>1.462</td>
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<td>3.882</td>
<td>0.129</td>
<td>0.119</td>
<td>0.112</td>
<td>0.119</td>
<td>0.089</td>
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</table>

Data collection:
- temperature/K: 100(2)
- no. of collected reflections: 39029
- within the θ-limit°: 0.96-25.00
- index ranges hkl: -24/18, -5/5, -51/51
- no. of unique reflections: 7063
- Rint: 0.0230

Refinement calculations: full-matrix least-squares on all F² values

<table>
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<tr>
<th>Weighting expression w</th>
<th>([σ²(F_c)+0.0125P]^{1/2} + 10.6157P]^{1/2})</th>
<th>([σ²(F_c)+0.0286P]^{1/2} + 2.0183P]^{1/2})</th>
<th>([σ²(F_c)+0.0396P]^{1/2} + 0.6319P]^{1/2})</th>
<th>([σ²(F_c)+0.0361P]^{1/2} + 0.5400P]^{1/2})</th>
<th>([σ²(F_c)+0.0420P]^{1/2} + 1.0797P]^{1/2})</th>
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<td>244</td>
<td>210</td>
<td>107</td>
<td>248</td>
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<td>no. of F values used [I&gt;2σ(I)]</td>
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<td>3660</td>
<td>2604</td>
<td>2410</td>
<td>1471</td>
<td>1955</td>
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</tbody>
</table>

Final R-Indices
- \(R_s(=\Sigma|ΔF|/|ΣF_s|)\): 0.0479
- \(wR(=\Sigma|F_o|^2)|\): 0.1082
- \(S(=\text{Goodness of fit on } F^2)\): 1.221
- \(\text{Final } Δρ_{max}/Δρ_{ave} / Å^{-3}\): 0.355/-0.493

\(P = (F_0^2 + 2F_c^2)/3\).
Structural studies

In order to collect information on the molecular geometries and packing behaviour in the solid state of bisphenols 1-8 their crystal structures have been determined. The crystal data is summarized in Table 1, selected conformational parameters and inter- and intramolecular contacts are listed in Table 2 and Table S2 (ESI), respectively. The X-ray structures of solvent-free 2,2'-methylenebis(4-nitrophenol) (1) as well as 2,2'-methylenebisphenol25 (8) and its 1:½ : ½ inclusion compound with H2O and DABCO26 (8a) has already been published and are included in our discussion for comparison reasons.

Table 2  Selected conformational parameters for the molecular structures of 1-8

<table>
<thead>
<tr>
<th>Compound</th>
<th>Caryl-Cbridge-Caryl angle (°)</th>
<th>Dihedral angle φ (°)</th>
<th>Pitch angle ψ (°)</th>
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<tr>
<td>1a</td>
<td>112.0(2)/112.7(2)</td>
<td>70.25(13)/69.64(13)</td>
<td>81.0(2); 87.0(2)/85.6(2); 78.8(2)</td>
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<tr>
<td>2a</td>
<td>109.8(2)</td>
<td>76.77(12)</td>
<td>83.8(2); 81.9(2)</td>
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<tr>
<td>4</td>
<td>113.92(9)</td>
<td>74.90(5)</td>
<td>72.61(11); 66.27(11)</td>
</tr>
<tr>
<td>5</td>
<td>114.26(12)</td>
<td>77.78(7)</td>
<td>68.05(16); 68.07(16)</td>
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<tr>
<td>6</td>
<td>115.11(14)</td>
<td>65.5(7)</td>
<td>75.6(9)</td>
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<td>7</td>
<td>115.6(2)</td>
<td>65.25(11)</td>
<td>77.4(2); 75.7(2)</td>
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<tr>
<td>8</td>
<td>113.65(7)</td>
<td>71.62(10)</td>
<td>75.6(2); 71.8(2)</td>
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<td>18</td>
<td>113.0/114.1</td>
<td>73.9/75.2</td>
<td>77.6; 71.7/73.4; 77.9</td>
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<tr>
<td>8a26</td>
<td>114.8</td>
<td>61.8</td>
<td>89.1; 88.1</td>
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a Dihedral angle between the planes of the aromatic units
b Angle between the plane of each aromatic unit and the plane defined by Caryl-Cbridge-Caryl

Crystallization of bisphenol 1 from dimethylsulfoxide yielded yellowish crystals of 1a which proved to be a 1:2 inclusion of 1 and DMSO in the monoclinic space group P21/n. The asymmetric unit contains two independent host and four guest molecules (Fig. 1a). Both bisphenols show more or less identical dihedral [70.25(13) ° / 69.64(13) °] and pitch angles [81.0(2) °; 87.0(2) ° / 85.6(2) °; 78.8(2) °] (Table 2). In both molecules of 1 the aromatic moieties are distorted to each other i.e. nitro and hydroxyl groups are placed oppositely. This arrangement is stabilized by one weak intermolecular C-H···O contact27 per independent molecule involving a phenol oxygen and an aromatic proton [d(H···O) = 2.57 Å / 2.56 Å]. By way of interest, two different species of guest molecules can be observed. Two of the DMSO molecules are connected via strong O-H···O bonds to phenolic oxygens of the host (O6 and O9) [d(H···O) = 1.80 Å / 1.81 Å]; a similar situation can be found in related DMSO inclusions.28 These strong H bonds are supported by weaker C-H···O contacts from the same DMSO oxygen atoms towards aromatic protons of rings B and C (inverse bifurcated H bond). The second type of DMSO guests are only connected via C-H···O contacts with host molecules, which could be the explanation of their disorder via the sulfur atom [S1IA/S1IB: 0.926(5)/0.074(5); S1KA/S1KB: 0.921(5)/0.079(5)].
In the overall packing of 1a, we found an interesting layered structure consisting of bisphenol and DMSO molecules arranged in an alternating manner. In detail, each host monolayer is formed by stacks of 1 in the direction of the crystallographic b axis developing π⋯π stacking with distance from 3.350(4) Å to 3.401(4) Å. The interconnection of the molecular stacks is realized by weak C-H⋯O contacts [d(H⋯O) = 2.50-2.54 Å]. In the guest monolayer, the dimethylsulfoxide molecules are interconnected by C-H⋯O contacts [d(H⋯O) = 2.50-2.56 Å] resulting in a helical arrangement in direction of the crystallographic b axis, parallel to the host piles. The distances of the DMSO guests to each other are comparable to those in the liquid structure of dimethyl sulfoxide.29 Host and guest monolayers are linked via a series of strong O-H⋯O hydrogen bonds [d(H⋯O) = 1.76-1.81 Å]. Furthermore, C-H⋯O contacts [d(H⋯O) = 2.47-2.67 Å] can be discussed (Fig. 2; Table S2, ESI).
Crystallization of the brominated bisphenol 2 from DMSO delivered colorless crystals of a 1:2 inclusion compound (2a) in the triclinic space group P-1. The asymmetric unit is displayed in Figure 1b. The C_aryl-C_{bridge}-C_aryl angle of the host in 2a is slightly smaller in comparison to 1a, whereas the dihedral angle is larger. The pitch angles of 2 are almost equal for both aromatic rings [83.9(2)° / 81.9(2)°], with the two phenolic groups being turned away from each other. Like in 1a, an intramolecular C-H···O contact [d(H···O) = 2.65 Å] was observed, which is in 2a accompanied by two OH···Br contacts [d(H···Br) = 2.63-2.64 Å].
As in 1a, the overall packing of 2a is featuring a layered structure consisting of bisphenol and DMSO molecules arranged in an alternating manner. However, the bulky bromine atoms prevent the formation of host badges, though induce stacks of bisphenol molecules arranged in a zig-zag manner running in direction of the crystallographic $a$ axis. Within the badges $\pi\cdots\pi$ \([d = 3.372(2) \text{ Å}]\) and C-H-\cdots$\pi$ interactions\(^{30,31}\) \([d(\text{H}\cdots\pi) = 2.88 \text{ Å}]\) prevail, which are supplemented by Br-\cdotsO contacts\(^{32}\) \([d(\text{Br}\cdotsO) = 3.309(2), 3.367(2) \text{ Å}]\) (Fig. 3). In comparison to 1a, the packing motif within the guest layer of 2a is somewhat different. Here, we found DMSO dimers connected \textit{via} C-H-\cdotsO bonds \([d(\text{H}\cdotsO) = 2.46-2.66 \text{ Å}]\) with an additional C-H-\cdotsS contact\(^{33}\) \([d(\text{H}\cdotsS) = 2.90 \text{ Å}]\) to link them.

Both the lamellar inclusion compounds 1a and 2a also display a pronounced foliated habitus of their crystals. These were rather difficult to prepare for the X-ray measurement due to their softness, with the respective layers able to easily slide against each other. This observation may be due to the high solvent content of the crystals and the weak forces between the lamina. It is
interesting to note that the mother compound 8 and phenyl substituted bisphenols are also known to form layered inclusion compounds.\textsuperscript{26, 34} In general, a number of layered inclusion compounds and complexes can be found, which is true for purely organic\textsuperscript{35} and hybrid systems.\textsuperscript{36} Furthermore, there are also a restricted number of DMSO intercalates described in the literature.\textsuperscript{37}

Pale yellow crystals of benzodioxine 4 suitable for X-ray diffraction have been obtained from chloroform and feature the monoclinic space group $P2_1/n$. The bisphenol skeleton develops a dihedral angle of 74.90(5)°, with pitch angles of 72.61(11)° for ring A and 66.27(11)° for ring B (Table 2). The atoms O3-C1-C2-C14 span a plane which is almost coplanar $[1.78(6)\text{°}]$ with the aromatic plane A. Atoms O7 and C15 deviate from this plane by -0.392(1) Å and 0.329(1) Å, respectively. For the second half of the molecule, we found a larger interplanar angle between ring B and O4-C8-C9-C16 $[5.49(7)\text{°}]$ and a different deviation of O8 $[0.230(1)\text{Å}]$ and C17 $[-0.543(1)\text{Å}]$ (Fig. 4a).

As depicted in Fig. 4b, the crystal packing of 4 is determined by moderately strong C-H···O contacts $[d(H\cdots O) = 2.43-2.54\text{Å}]$. By way of interest, only the methylene bridges connecting the aromatic units and those of the acetals act as H donors and most of the oxygen atoms of the nitro groups and the acetal moieties act as H acceptors.

In order to elucidate the reasons for the resistance of bisacetal 4 towards acidic hydrolysis, we studied its bond lengths and angles in the crystal and compared them with related compounds. As a crystal structure of the acetylated monomer 9, which undergoes the respective hydrolysis readily\textsuperscript{24}, is not available in the literature we included the simple monomer 10\textsuperscript{38} in our comparison accompanied by the isopropylidene protected bisphenol 11\textsuperscript{39} (Scheme 2). Acetonides like 11 are known for their facile cleavage under acidic conditions.\textsuperscript{40} As shown in
Table 3, the values of the equivalent bond lengths and angles of 4, 10 and 11 differ only slightly. The largest differences can be observed for the bond lengths a and c. These are much shorter in 4 and 10 in comparison to 11, which may explain the lack of reactivity of 4 towards hydrolysis.

<table>
<thead>
<tr>
<th>Bond lengths (Å)</th>
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<tr>
<td>b / b'</td>
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<td>1.434</td>
<td>1.441 / 1.444</td>
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<tr>
<td>c / c'</td>
<td>1.3909(13) / 1.3992(14)</td>
<td>1.377</td>
<td>1.421 / 1.411</td>
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<tr>
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<td>1.444 / 1.438</td>
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<td>1.501</td>
<td>1.506 / 1.500</td>
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</tbody>
</table>

<table>
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<th>angle (°)</th>
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<td>114.9 / 115.5</td>
</tr>
<tr>
<td>b-c / b'-c'</td>
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<td>c-d / c'-d'</td>
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<td>d-e / d'-e'</td>
<td>110.36(9) / 110.77(10)</td>
<td>109.9</td>
<td>111.2 / 111.4</td>
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</table>

Etherification of 1 delivers the more lipophilic dimethoxyether 5, though the molecular conformation between educt and product differs only slightly (Table 2). The two dimethoxy groups in 5 are in distal positions (Fig. 5), resulting in a dihedral angle of 77.78(7) ° for the respective aromatic units. Worth mentioning are the relatively small pitch angles of both phenyl rings [68.05(16) °; 68.07(16) °]. The methoxy group creates a rather non-polar compound which lacks strong interactions in the overall packing. Nevertheless, C-H···O contacts involving the ether and nitro oxygen atoms and methylene/methyl hydrogens are obvious [d(H···O) = 2.44-2.54 Å] (Table S2, ESI).

**Fig. 5** Molecular structure of 5, shown with 50 % displacement probability displacement ellipsoids.
Crystallization of diester 6 from \textit{n}-hexane/ethyl acetate (1:1) gives orthorhombic crystals in the space group \textit{Fdd2}; the asymmetric units contains only half a molecule. The dihedral angle is 65.5(7) °, being considerably lower than for the above discussed nitro bisphenols (Table 2); the pitch angle is 75.6(9) °. As displayed in Fig. 6a, the phenol moieties are in distal positions and the carbonyl groups of the COOMe pendants are almost coplanar with respect to the aromatic plane [torsion angle: C5-C4-C8-O2 = -8.4(2) °].

The introduction of two formyl moieties into 6 delivers bisaldehyde 7, whereas the molecular conformation is more or less unchanged [dihedral angle: 65.25(11); pitch angle: 77.4(2) ° / 75.7(2) °] (Table 2, Fig. 6b). All four carbonyl groups of 7 are nearly coplanar with reference to the benzene rings [torsion angles: C5-C4-C15-O3 = -6.5(4) °, C12-C11-C18-O7 = -175.9(3) °; C1-C2-C14-O2 = 1.3(4) °, C8-C9-C17-O6 = -1.9(4) °]. This conformation is stabilized by a weak C-H···O contact between the ester moieties and an aromatic proton. (Such a contact can also be observed for 6, but with much lower angles, therefore we did not describe it there.) Both formyl groups are engaged into a strong hydrogen bond with the neighboring OH group in \textit{ortho} position. The H···O distances are 1.89 and 1.90 Å, which is only slightly longer than the analogue H-bond in the \textit{tert}-butyl derivative\textsuperscript{41} [d(H···O) = 1.85 Å].

![Molecular structures of 6 (a) and 7 (b), shown with 50 % displacement probability displacement ellipsoids. Packing arrangements of 6 (c) and 7 (d) are shown viewing down the crystallographic \textit{a} axes. (Broken lines represent hydrogen bonds/contacts.)](image)

The high molecular similarity of 6 and 7 does also lead to a related packing behavior, which is in both cases dominated by the formation of molecular batches. These piles show typical distances between the aromatic moieties of bisphenol molecules such as 3.441(2) Å for 6 as
well as 3.379(3) Å and 3.481(3) Å for 7. Their interconnections are in both cases accomplished by a combination of strong O-H···O [d(H···O) = 1.89 Å] and weak C-H···O bonds [d(H···O) = 2.39-2.55 Å]. However, the high conformational similarity of 6 and 7 (Table 2) does not lead to a completely analogue packing behavior: In the structure of 6, the phenolic hydroxyl function (H donor) and the ester carbonyl (H acceptor) are engaged in the strong H bond; the methyl group of the ester (H donor) and the phenol oxygen (H acceptor) display a weak C-H···O bond. In 7, two molecules are connected pairwise via a strong O-H···O bond (inverse bifurcated H bond), whereas only one of two possible phenol-aldehyde rings is involved.

To enable a better comparison with the decorated bisphenols 1-7, we re-determined the X-ray structure of mother compound 8 and included the respective data in our considerations. By way of interest, it is the only bisphenol discussed here in which the phenolic unit are not distorted to each other but are placed on the same side of the molecule. This fact leads to the strong intermolecular hydrogen bonds [d(H···O) = 1.92-2.02 Å] also described in the literature. Additionally, we have been able to determine a series of intermolecular C-H···π interactions with H···π distances between 2.63 and 2.95 Å. Furthermore, π···π contacts can be discussed [d(centroid B···centroid B) = 3.343(2) Å] (Fig. 7).

**Comparison of bisphenols 1, 2 and 4-8**

Except for mother compound 8, distorted aromatic moieties were found in the molecular structures of all bisphenols studied here. This is indifferent to the influence of competing solvents (1a, 2a), substitution of the phenol groups (4, 5) or H bond acceptors attached to the
benzene rings (7). Even for 6, the steric demands of the COOMe groups seem to overcompensate the expected formation of O-H···O bonds. Hence it seems feasible to state that the opposite orientation of the decorated bisphenols occurs regardless of their substituents. The dihedral angles of the bisphenols discussed in this paper range from 65.3 for 7 to 77.8 ° for 5. By way of interest, the bisphenol ester 6 and its formyl derivative 7 display very similar conformations, which is true for the dihedral angles as well as for the C-aryl-Cbridge-C-aryl and the pitch angles (Table 2). Of note is that the bisphenol in 2a has the smallest, and the one in 7 the largest C-aryl-Cbridge-Caryl angle – both are bisphenols with two deactivating groups at one benzene ring.

In the following, we evaluated the influence of substituents at the bisphenol to the general packing behavior. Mother compound 8 displays disordered OH hydrogen atoms and develops long, strand-like molecular arrangements featuring extensive edge-to-face contacts (C-H···π) between the bisphenol molecules, which are also interconnected via strong O-H···O hydrogen bonds. Interestingly, both features are also found in bisphenol F₄² representing an isomer of 8. As depicted in Fig. 8, the introduction of substituents to the aromatic moieties changes the intermolecular interactions into face-to-face contacts resulting either in bisphenol stacks (1a, 6, 7) or handshake-like motifs between two bisphenol molecules (2a, 4, 5). The latter seems to be preferred for bisphenols with more or less bulky substituents (Me, CH₂OCH₂) at or near the phenolic oxygen, while free OH-groups seem to favor the face-to-face stacking. However, mother bisphenol 1⁸ develops a hand-shake motif and no piles of molecules as 1a, whereas in 8a⁶ the intercalation of guests in between the hydrogen bonding system can be observed.
Measurement of $K_{\text{assoc}}$ between bisphenols 1-7 and DMSO

Since bisphenols 1 and 2 formed solvates with DMSO it was important to ascertain if the interactions observed occur also in solution, or whether they were artefacts introduced by the crystallization procedure. Proton NMR was used to establish the binding coefficients between the bisphenols and DMSO in solution; for comparison reasons we also included title compounds 3-7.

Only bisphenols 1, 6 and 7 were found to form medium strong complexes with DMSO in solution (Figure 9, Table 4), with the rest showing no evidence of interaction. The binding of bisphenols 1, 6 and 7 to DMSO was in fast exchange on the NMR time-scale, and was
characteristic of a 1:1 binding. All of the bisphenols that exhibited interactions contained hydroxyl groups at positions 1 and 8, and therefore it is likely that these groups and the polar DMSO account for the complexation. Like in the X-ray structure of 1, the interaction with DMSO can be attributed to strong O-H···O hydrogen bonds (Figure 1), which seems feasible for 6 and 7 as well. Bisphenol 2 also contains phenolic hydroxyl groups, however the NMR signal for these protons was so broad that it precluded accurate measurement.

![Graph showing binding isotherms](image)

**Fig. 9** Binding isotherms observed during the titration of DMSO into solutions containing selected bisphenols. The OH protons of bisphenols 1, 6 and 7 were tracked through the course of the titration. Error bars represent the RMS of the fitted curve.

<table>
<thead>
<tr>
<th>Bisphenol</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{assoc}$ (M$^{-1}$)</td>
<td>1.01</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>5.26</td>
<td>3.13</td>
</tr>
</tbody>
</table>

* not determined

**Conclusion**

Acid-catalysed dimerization of putative derivatized phenols followed by subsequent substitution reactions delivered the title compounds 1-7. Their respective molecular structures and packing behaviors have been studied by X-ray diffraction, comparatively discussed and put into relation with the unsubstituted bisphenol 8. The dihedral angles of the bisphenols studied in this paper range from 65.3 to 77.8 °. Thereby, we have been able to pinpoint a certain tendency for small or large angles in bisphenols with two deactivating groups at one benzene ring. Except for mother compound 8, in the molecular structures of all bisphenols studied here distorted aromatic moieties were found. Hence, the substituents probed here prevent proximal position of phenolic units and the formation of strong O-H···O hydrogen bonds.

In the packing of mother compound 8 we found a strand-like molecular arrangement featuring strong O-H···O hydrogen bonds and extensive edge-to-face contacts (C-H···π) between the bisphenol molecules. The introduction of substituents to the aromatic moieties is changing this intermolecular interactions into face-to-face contacts resulting either in bisphenol stacks (1a, 6,
or handshake-like motifs between two bisphenols (2a, 4, 5). In both cases, the C-H···π interactions are more or less replaced by C-H···O contacts as the prevalent non-covalent interaction in the packing, which is likely to be connected with the decreasing electron density on the phenol rings. The two nitro bisphenols 1 and 2 in their DMSO inclusion compounds presented here feature an exciting layered arrangement. NMR titrations suggest that at least for 1 the strong O-H···O hydrogen bonds between the phenolic hydroxyl groups and DMSO also occur in solution and are no crystallization artefacts. However, the weaker contacts found in the X-ray structure could not be confirmed by solution NMR. Both the lamellar inclusion compounds 1a and 2a display also a pronounced foliated habitus of their crystals. Such a layer formation has already been observed for the unsubstiuted mother bisphenol. Hence, this type of molecules represent an auspicious tectone for crystal engineering with promising macroscopic properties and applications within materials chemistry.

**Experimental Section**

**Methods and Materials**

The melting points were measured on a microscope heating stage PHMK Rapido (VEB Dresden Analytik) and are uncorrected. 1H and 13C NMR spectra were obtained from a Bruker Avance 500 at 500.1 (1H) and 125.8 MHz (13C) using TMS as internal standard. Chemical shifts for proton and carbon resonances are given in ppm (δ). Signal multiplicity is characterized by s (singlet), d (doublet) and dd (double doublet). Mass spectra were recorded on a Hewlett Packard 5890 Series II/MS 5971 A. IR spectra were measured on a Nicolet ATR-FT-IR 510 as KBr pellets and with the ATR method, respectively. Analytical TLC was performed on pre-coated silica gel plates (60 F254, Merck).

4-Nitrophenol and methyl iodide were purchased from Acros Organics, methyl 4-hydroxybenzoate from Fluka, formaldehyde from Chemsolute, and bisphenol 8 from Aldrich. The chemicals were used as received without further purification. Organic solvents were purified and dried (where necessary) by standard procedures. The synthesis and analytical characterization of compounds 15 and 60 have already been described in the literature; we present here their full spectroscopic characterization.

**Syntheses**

2,2'-Methylenebis(4-nitrophenol) (1). In a 250 ml three-neck flask with a mechanical stirrer 4-nitrophenol (27.83 g, 200.1 mmol) was heated together with 5 ml of water at 90 °C. To the resulting liquid phase a mixture of an aqueous solution of formaldehyde (37 %, 9.46 ml, 127.0 mmol) and concentrated sulphuric acid (10 ml) was added dropwise. The pale yellow suspension was heated for 2.5 h at 110 °C and after that 3 h at room temperature. Subsequently, the supernatant liquid was heated to give 24.83 g (13.5 mmol). IR (ATR): 3582, 3258, 3052,
1588, 1472, 1431, 1335, 1305, 1207, 1125, 1088, 959, 916, 836, 786, 748, 720. m/z (ESI⁺) = 312.83 [M+Na]⁺, calc. 313.22.

6,6'-Methylenebis(2-bromo-4-nitrophenol) (2). To a solution of boric acid (42.80 mg, 692.2 μmol) in ethanol (35 ml), hydrogen peroxide (30 %, 4.74 ml, 46.40 mmol), 2,2'-methylenebis(4-nitrophenol) (1) (2.00 g, 6.90 mmol), potassium bromide (1.81 g, 15.21 mmol) and sulfuric acid (5 ml, 20.0 ml) were added. The resulting mixture was stirred at room temperature for 20 h and finally extracted with MTBE (3x). In order to destroy excessive H₂O₂, the combined organic phases were washed with saturated Na₂SO₃ solution, followed by water. The organic phase was dried over sodium sulfate, with the solvent being subsequently removed to yield a pale yellow solid. Yield 92 % (2.84 g). M. p. 251-253 °C (Sublimation). Rf = 0.49 [SiO₂; n-hexane/ethyl acetate (8:2)]. ¹H NMR (500 MHz, DMSO-d₆) δ = 4.13 (s, 2H, ArCH₂Ar), 8.04 (d, ²J = 2.7 Hz, 2H, 5,5'-ArH), 8.28 (d, ³J = 2.6 Hz, 2H, 3,3'-ArH). ¹³C NMR (125 MHz, DMSO-d₆) δ = 31.8 (ArCH₂Ar), 110.7 (2,2'-ArC), 125.1 (3,3'-ArC), 127.0 (5,5'-ArC), 128.7 (6,6'-ArC), 139.1 (4,4'-ArC), 159.7 (1,1'-ArC). IR (ATR): 3245, 2998, 1574, 1526, 1459, 1355, 1345, 1150, 1090, 970, 978, 815, 760. m/z (ESI) = 446.8 [M⁻H]⁻, calc. 447.0.

Bis(6-nitro-4H-benzo[d][1,3]dioxin-8-yl)methane (4). 2,2'-Methylenebis(4-nitrophenol) (1) (5.00 g, 17.23 mmol) was added to an aqueous solution of formaldehyde (37 wt %, 5.36 ml, 71.98 mmol) and heated to 90 °C. A mixture of 15.0 ml concentrated sulfuric acid and 4.0 ml of water was added dropwise to the hot solution. The resulting pale yellow suspension was heated for an additional hour. After cooling to room temperature the precipitate formed was filtered off and washed with a diluted sodium hydroxide solution to obtain a pale yellow solid. Yield 70 % (4.51 g). M. p. 222-224 °C (lit.:¹⁸ 225 °C). Rf = 0.55 [SiO₂; n-hexane/ethyl acetate (7:3)]. ¹H NMR (500 MHz, DMSO-d₆) δ = 3.99 (s, 2H, ArCH₂Ar), 5.01 (s, 4H, ArCH₂O), 5.42 (s, 4H, OCH₂O), 7.87 (s, 2H, 7,7'-ArH), 8.01 (s, 2H, 5,5'-ArH). ¹³C NMR (125 MHz, CDCl₃) δ = 27.9 (ArCH₂Ar), 65.4 (ArCH₂O), 91.8 (OCH₂O), 120.5 (5,5'-ArC), 122.2 (4a,4a'-ArC), 123.6 (7,7'-ArC), 127.6 (8,8'-ArC), 140.4 (6,6'-ArC), 155.7 (8a,8a'-ArC). IR (KBr): 3076, 2869, 1617, 1593, 1514, 1465, 1339, 1269, 1239, 1155, 1083, 1003, 952, 907, 809, 779, 747, 732, 702. m/z (ESI) [M⁻H]⁻ 373.7, calc. 373.3.

2,2'-Methylenebis(4-nitroanisole) (5). Bisphenol 1 (4.00 g, 13.78 mmol), potassium carbonate (20.40 g, 147.6 mmol) and methyl iodide (9.0 ml, 144.9 mmol) were added to a solution of 800 ml acetonitrile and 200 ml dimethylformamide. The resulting pale yellow suspension was refluxed for 5 h and then acetonitrile was removed under vacuum. Afterwards, hydrochloric acid (1 ml, 500 ml) was added to the residue, then the precipitate formed was filtered off and dried in vacuo. Yield 95 % (4.15 g). Mp 183-185 °C (lit.:¹³ 185-189 °C). Rf = 0.77 [SiO₂; n-hexane/ethyl acetate (7:3)]. ¹H NMR (500 MHz, CDCl₃) δ = 3.96 (s, 6H, CH₃), 4.01 (s, 2H, ArCH₂Ar), 6.94 (d, ⁴J = 9.1 Hz, 2H, 6,6'-ArH), 8.02 (d, ⁴J = 2.8 Hz, 2H, 3,3'-ArH),
8.16 (dd, 2H, \(^4J = 2.8\) Hz, \(^3J = 9.1\) Hz, 5,5'-ArH). \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 30.4 (ArCH\(_2\)Ar), 56.2 (CH\(_3\)), 110.0 (6,6'-ArC), 124.4 (5,5'ArC), 126.0 (3,3'-ArC), 128.7 (2,2'-ArC), 141.4 (1,1'-ArC), 162.5 (1,1'-ArC). IR (ATR) 1608, 1588, 1514, 1493, 1458, 1339, 1260, 1182, 1142, 1094, 1015, 950, 908, 891, 830, 817, 765, 750. \(m/z [M]^+\) 318, calc. 318.

**Dimethyl 3,3'-methylenbis(4-hydroxybenzoate)** (6). Methyl 4-hydroxybenzoate (40.00 g, 262.9 mmol) was suspended in 350 ml of 50 % (v/v) sulphuric acid and heated to 85 °C. An aqueous solution of formaldehyde (37 wt %, 4.17 ml, 56.00 mmol) was added and the mixture heated for 2 h. The resulting precipitate was filtered, washed thoroughly with water and dried in vacuo. Finally the crude product was washed three times with 300 ml of ethyl acetate and dried afterwards to obtain 15.42 g (87 %) of a white solid. M. p. 282-284 °C (lit.\(^43\) 277-280 °C). \(R_f = 0.48\) [SiO\(_2\); n-hexane/ethyl acetate (6:4)]. \(^1^H\) NMR (500 MHz, DMSO-d\(_6\)) \(\delta\) 3.75 (s, 6H, CH\(_3\)), 3.86 (s, 2H, ArCH\(_2\)Ar), 6.91 (3, \(^3J = 8.5\) Hz, 2H, 5,5'-ArH), 7.64 (d, \(^4J = 2.2\) Hz, 2H, 2,2'-ArH), 7.70 (dd, \(^4J = 2.2\) Hz, \(^3J = 8.5\) Hz, 2H, 6,6'-ArH), 10.44 (s, 2H, Ar-OH). \(^1^3\)C NMR (125 MHz, DMSO-d\(_6\)) \(\delta\) 29.1 (ArCH\(_2\)Ar), 51.5 (CH\(_3\)), 114.8 (5,5'-ArC), 120.2 (1,1'-ArC), 126.7 (3,3'-ArC), 129.1 (6,6'-ArC), 131.6 (2,2'-ArC), 159.9 (4,4'-ArC), 166.2 (C=O). IR (KBr): 3279, 2960, 1677, 1600, 1506, 1445, 1434, 1353, 1276, 1222, 1192, 1168, 1131, 1100, 992, 924, 902, 828, 767. \(m/z\) (ESI\(^+\)) 339.9 [M+Na]\(^+\), cal. 339.3.

**Dimethyl 5,5'-methylenbis(3-formyl-4-hydroxybenzoate)** (7). To a suspension of dimethyl 3,3'-methylenbis (4-hydroxybenzoate) (6) (10.00 g, 31.61 mmol) in 150 ml of trifluoroacetic acid was added hexamethylenetetramine (38.40 g, 273.9 mmol). This mixture was refluxed for 24 h before the resulting yellow solution was poured in 500 ml of water and stirred for 1 h at room temperature. The solid formed was filtered off, washed with a small amount of water and dried in vacuo to obtain a white powder. Yield 88 % (10.36 g). M. p. 204-206 °C. \(R_f = 0.59\) [SiO\(_2\); n-hexane/ethyl acetate (6:4)]. \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.91 (s, 6H, CH\(_3\)), 4.09 (s, 2H, ArCH\(_2\)Ar), 8.14 (d, \(^4J = 2.1\) Hz, 2H, 6,6'-ArH), 8.21 (d, \(^4J = 2.1\) Hz, 2H, 2,2'-ArH), 9.93 (s, 2H, Ar-OH), 11.74 (s, 2H, CHO). \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 28.1 (ArCH\(_2\)Ar), 51.8 (CH\(_3\)), 119.4 (3,3'-ArC), 121.5 (1,1'-ArC), 127.8 (5,5'-ArC), 134.2 (2,2'-ArC), 138.0 (6,6'-ArC), 162.8 (4,4'-ArC), 165.3 (C=O), 196.0 (CHO). IR (KBr): 3084, 2951, 2881, 1729, 1710, 1650, 1616, 1596, 1431, 1395, 1362, 1314, 1278, 1219, 1198, 1113, 1020, 995, 921, 901, 764, 714, 703. \(m/z\) (ESI\(^+\)) 370.9 [M-H]\(^-\), calc. 371.3.

**X-ray crystallography**

Crystals of compounds 1a, 2a and 3-8 suitable for X-ray diffraction have been obtained by slow evaporation of respective solutions (1 and 2 in DMSO, 3, 4 and 5 in chloroform, 6 and 7 in n-hexane/ethyl acetate, 8 in benzene). The crystal quality of 3 proved to be insufficient for publication.

The intensity data have been collected at 100 K on a Bruker Kappa diffractometer equipped with an APEX II CCD area detector and graphite-monochromatized MoK\(_\alpha\) radiation (\(\lambda = 0.71073\) Å) employing \(\varphi\) and \(\omega\) scan modes. The data have been corrected for Lorentz and polarization effects. Semi-empirical absorption correction was applied using the SADABS program.\(^44\) The SAINT program\(^44\) has been used for the integration of the diffraction profiles. The crystal structures were solved by direct methods using SHELXS-97\(^45\) and refined by full-matrix least-squares refinement against \(F^2\) using SHELXL-97.\(^45\) All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were positioned geometrically and allowed to ride on their parent atoms. Geometrical calculations were performed using PLATON and molecular graphics were generated using SHELXTL.\(^45\) The crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre; CCDC numbers:
NMR spectrometry

Saturated solutions of bisphenols 1-7 were prepared in deuterated acetonitrile, and their concentrations determined using quantitative NMR against a solution of known concentration. NMR was performed using a Bruker Avance III 500 MHz spectrometer equipped with a room-temperature probe at 300 K. $^1$H spectra were recorded using 128k complex points and a recovery time of 4 s. 16 transients were generally sufficient to achieve good signal-to-noise, however this was increased to 64 for the less soluble molecules. DMSO was titrated into the bisphenol solutions at the following (v/v) ratios: 0.002; 0.004; 0.008; 0.016; 0.039; 0.075; 0.139; and 0.287. The chemical shift perturbation (CSP) of each peak was elucidated at each titration point, and the binding constants of significantly perturbed peaks ascertained according to the literature. 46

Acknowledgement

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References


17 By treating 1 with bromine and powdered iron (analogous to Y.-Y. Liu and M. Minich, J. Labelled Compd. Radiopharm., 1981, 18, 791-797.), we were able to observe double bromination of the methylene bridges.


